Death and respiratory arrest related to ultra-rapid metabolism of codeine to morphine

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Agenda

- Background
- Medical literature
- AERS data
- Efforts to identify other cases
- Drug utilization
- Regulatory actions

Prior FDA Actions relating to ultra-rapid metabolism (UM) of codeine

- August 2007:
  - *Press release and public* health advisory – "Use of Codeine By Some Breastfeeding Mothers May Lead To Life-Threatening Side Effects In Nursing Babies"
  - Labeling of codeine-containing products updated to describe this risk

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Medical Literature: Codeine toxicity in ultra-rapid metabolizers

- Four articles described 7 pediatric patients who experienced codeine overdose and/or death and reported CYP2D6 status; these 7 cases were also reported in AERS.

- 2007 Voronov et al (Ped Anesthesia)
  - 29-month old of North African descent received codeine/APAP post AT for recurrent tonsillitis and mild-moderate sleep apnea; found unresponsive on evening of postop day 1; resuscitated
    - EM-UM by genotype

- 2009 Ciszkowski et al (NEJM)
  - 2 yr old received codeine/APAP after AT for obstructive sleep apnea syndrome (OSA); died on postop day 2
    - UM by genotype

Medical literature: codeine (2)

- 2012 Kelly et al (Pediatrics)
  - 4 yr old boy received codeine post AT for OSA and recurrent tonsillitis; died on postop day 2
    - UM by genotype
  - 5 yr old boy received codeine/APAP post AT for recurrent tonsillitis and snoring; died on postop day 1
    - Likely UM by high blood morphine concentration relative to codeine
  - 3 yr old girl of Middle Eastern descent received codeine/APAP post AT for OSA; found unresponsive on postop day 2; resuscitated at hospital.
    - EM by genotype; morphine level consistent with UM phenotype

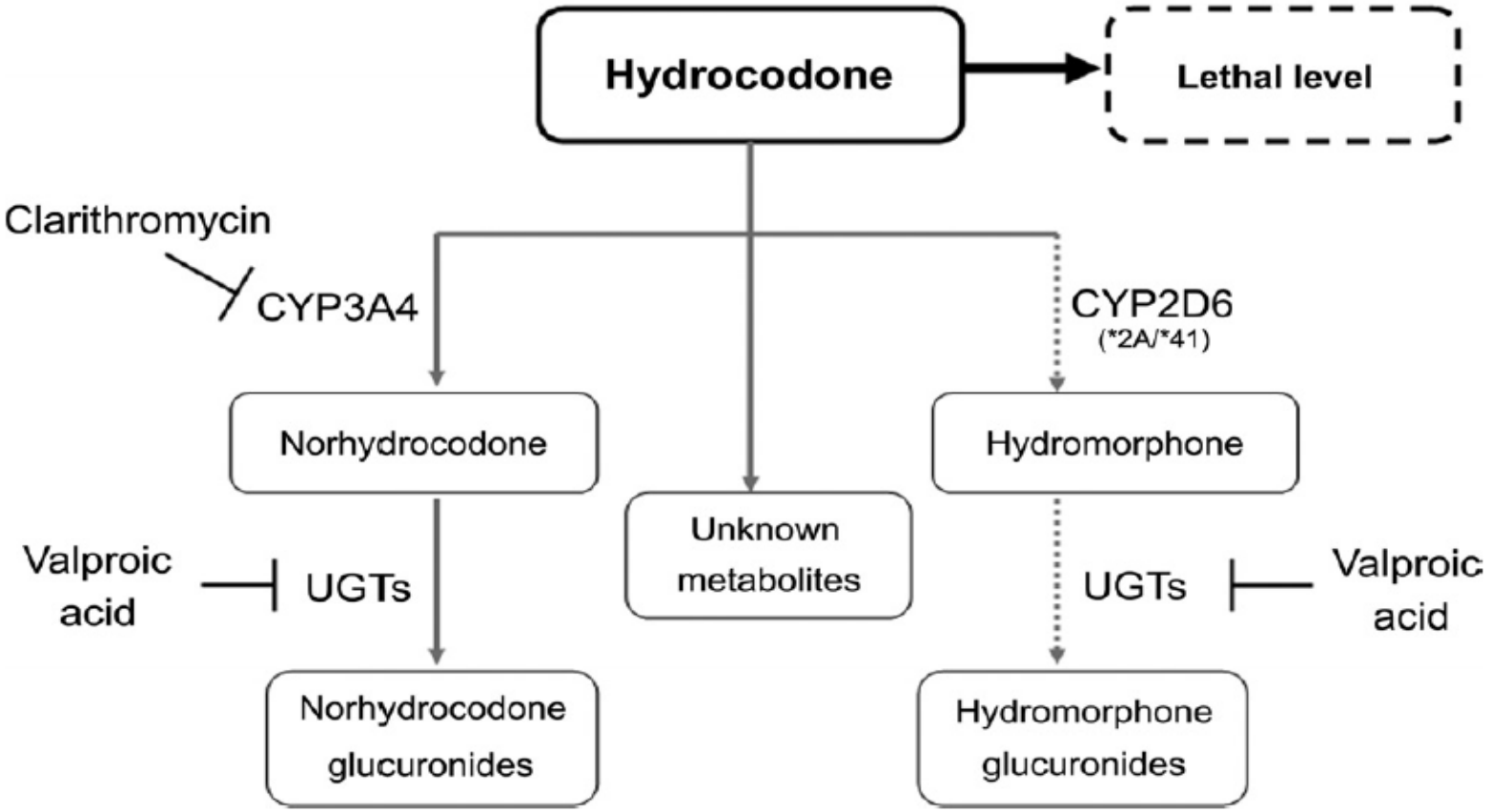
Medical literature: codeine (3)

- 2008 Hermanns-Clausen et al (Eur J Peds)
  - 3 yr old twins received codeine drops for cough, once daily x 6 days. One twin died; the second twin was found apneic and was resuscitated.
    - EM by genotype
    - Analysis of size of drops suggested possibility of inadvertent overdose

Literature Findings – other opioids

- 2010 Madadi et al (Pediatrics)
  - 6 yr old prescribed hydrocodone and clarithromycin for a cold and ear infection; found unresponsive on day 2 (had received 2x prescribed dose in 24 hours)
  - Little to no detectable CYP2D6 activity (PM)
  - Clarithromycin is an inhibitor of CYP3A4

Literature Findings



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AERS review - codeine

- The 7 literature cases accounted for the 7 AERS cases that mentioned CYP2D6 status
- The 6 other AERS cases are summarized below

	Death (n=6) without mention of CYP2D6
Age	Mean: 7.5 YR Median: 3 YR Range: 2-9 YR
Gender	Male (2) Female (3) Unknown (1)
Report year	2003 (1) 2005 (1) 2006 (1) 2010 (2) Unknown (1)
Country of occurrence	United States (4) Foreign (1) Unknown (1)
Report type	Expedited (6) Literature (none)
Outcome	Death (6)
Indications	Pain post AT (3), Oral Aphthae (1) Cough (1), Unknown (1)
Dose	Range: 0.4-1 mg/kg/dose; (N=3) mean: 0.6mg/kg/dose Unknown dose (N=3)
Time to onset	Mean: 39 hours Median: 48 hours Range: 1-48 hours (N=5)

AERS review- other opioids

- Review of the AERS database did not recover robust cases of unexplainable or unconfounded death or opioid toxicity following use of oxycodone, hydrocodone, or morphine in pediatric patients.

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Summary of information from American Academy of Otolaryngology survey*

- The Patient Safety and Quality Improvement Committee of the AAO-HNS surveyed physician membership regarding bad outcomes following tonsillectomy, such as death or permanent disability.
- Results of survey in press, but summary data shared regarding cases related to narcotics
- 8 pediatric cases classified as being related to narcotic medications
  - Indication: OSA (7), chronic tonsillitis (1)
  - Underlying condition: Down's syndrome (3), neurologic disorder (1)
  - Outcome: deaths (7), anoxic brain injury (1)
  - UM status: suspected due to high morphine levels (1), confirmed in post-mortem exam (1)

*Goldman JL, Baugh RF, Davies L, et al. Mortality and major morbidity after tonsillectomy: etiologic factors and strategies for prevention. Laryngoscope 2013. In press.

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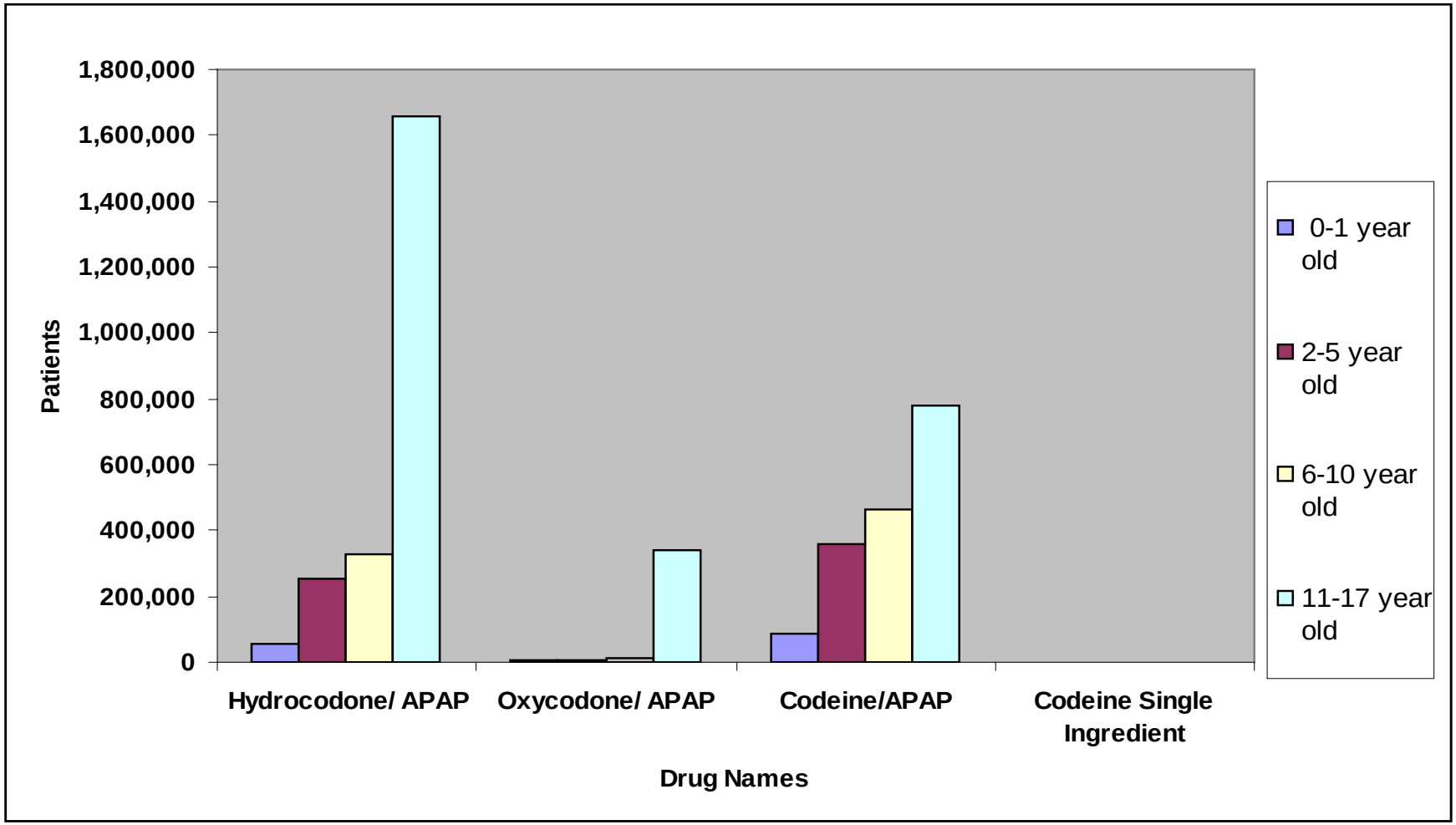
Nationally Estimated Number Of Pediatric Patients (0-1, 2-5, 6-10,11-17 year old) Receiving Dispensed Prescription for Selected Opioids from U.S. Outpatient Retail Pharmacies, Year 2011

Source: IMS, Total Patient Tracker, Extracted Sept, 2012



Codeine/Acetaminophen and Single-Ingredient Codeine Prescribing Specialty

Year 2007-2011, cumulative[1]

- General Practice/Family Medicine/Doctor of Osteopathy was the top prescribing specialty for:
  - codeine/acetaminophen (oral solid formulation)
  - codeine single-ingredient (oral liquid and solid formulations)
- Ear, Nose & Throat was the top specialty for:
  - codeine/acetaminophen (oral liquid formulation)
- Pediatricians accounted for:
  - 2% codeine/acetaminophen (oral solid)
  - 13% codeine/acetaminophen (oral liquid)
  - 2% codeine single-ingredient (oral solid)
  - 18% codeine single-ingredient (oral liquid)

[1]IMS, Vector One®: National VONA, Year 2007-2011 cumulative, extracted July 2012

Percentage of Prescriptions Dispensed for Codeine Containing Products and Comparators, (Prescribing Specialties) Through U.S. Outpatient Retail Pharmacies, Years 2007-2011, cumulative

Source: IMS, Vector One®:National, Extracted July and September 2012

	Codeine/APAP		Codeine Sulfate		Hydrocodone/APAP		Oxycodone /APAP		Morphine IR	
	Oral Solids	Oral Liquids	Oral Solids	Oral Liquids	Oral Solids	Oral Liquids	Oral Solids	Oral Liquids	Oral Solids	Oral Liquids
	Share %	*Share %*	*Share %*	*Share %*	*Share %*	*Share %*	*Share %*	*Share %*	*Share %*	*Share %*
General Practice/Family Medicine/Osteopathy	21.4%	10.1%	23.2%	23.2%	25.8%	11.3%	18.7%	5.9%	22.1%	32.4%
Dentist	19.4%	13.3%	0.70%	0.0%	10.2%	5.5%	5.3%	4.8%	0.1%	0.1%
Internal Medicine	14.6%	2.7%	22.0%	4.1%	14.2%	5.2%	12.5%	5.0%	14.0%	26.9%
Unspecified	6.0%	8.7%	6.6%	3.3%	5.6%	6.3%	5.9%	7.9%	7.7%	6.1%
Emergency Medicine	4.5%	9.8%	1.6%	5.2%	5.4%	7.2%	7.5%	2.7%	0.8%	1.2%
Obstetrics/Gynecology	4.3%	0.4%	1.1%	0.0%	1.9%	0.6%	4.4%	0.9%	0.3%	0.4%
Orthopedic Surgery	4.2%	3.3%	1.9%	2.9%	8.5%	2.4%	8.9%	2.0%	0.9%	0.2%
Physician Assisstant	3.3%	4.1%	2.7%	5.3%	3.9%	3.4%	5.0%	4.6%	4.0%	1.2%
Nurse Practitioner	2.8%	2.9%	4.3%	1.9%	3.4%	2.6%	3.6%	3.0%	6.4%	3.0%
Pediatrics	1.9%	12.7%	1.9%	17.8%	0.8%	4.8%	0.7%	3.8%	0.9%	1.4%
Ear/Nose/Throat (Orolaryngology)	1.3%	19.6%	0.5%	4.2%	0.6%	29.7%	0.6%	28.3%	0.0%	0.0%
All Others	16.3%	12.4%	33.5%	32.1%	19.7%	21.0%	26.9%	31.1%	42.7%	27.1%

Codeine/Acetaminophen Diagnosis Data Year 2007–2011, cumulative[1]

- "Surgery Follow-Up" (ICD-9 code V67.0) was the most common diagnosis code associated with the use of codeine/acetaminophen in all age groups.
- Indications of "Acute Tonsillitis" (ICD-9 code 463.0) and "Ch Tonsillitis & Adenoids" (ICD-9 474.0) in pediatrics aged 0-1 years, 2-5 years, 6-10 years, and 11-17 years, although low, were also mentioned.

[1]Encuity: Physician Drug and Diagnosis with Pain Panel. Year 2007 through 2011. Data Extracted July, 2012

Diagnosis Data for Hydrocodone/Acetaminophen, Oxycodone/Acetaminophen and Morphine Sulfate,

Year 2007–2011, cumulative[1]

- **Hydrocodone/Acetaminophen:**
  - "Tonsils with Adenoids Hypertrophy" (ICD-9 code 474.1) and "Acute Tonsillitis" (ICD-9 code 463.0) associated with 5% of the total drug use mentions in patients 0-1 year old.
  - The most common diagnosis among patients aged 2-5 years was "Tonsils with Adenoids Hypertrophy" (ICD-9 code 474.1) with 17% of the total drug use mentions
  - The most common diagnosis among patients aged 6-10 years was "Ch Tonsillitis & Adenoids" (ICD-9 474.0) with 11% of total use mentions

- **Oxycodone/Acetaminophen:**
  - "Ch Tonsillitis & Adenoids" (ICD-9 474.0) was associated with 1.5% of the total drug use mentions in pediatric patients aged 11-17 years old.
  - There were no diagnosis codes captured for conditions related to tonsillectomy in pediatric patients (0-1, 2-5, 6-10)

- **Morphine Sulfate:**
  - There were no diagnoses codes captured for conditions related to tonsillectomy among pediatric patients aged 2-5 year old, 6-10 year old and 11-17 years old.

[1]Encuity: Physician Drug and Diagnosis with Pain Panel. Year 2007 through 2011. Data Extracted September, 2012

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Regulatory Actions

- Labeling Changes- all codeine containing products (pain, cough/cold)
  - Boxed warning

WARNING: Death Related to Ultra-Rapid Metabolism of Codeine to Morphine

Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism

  - Contraindication

Codeine sulfate is contraindicated for postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy

  - Modifications to Warnings, Pediatric Use, Patient Counseling Information sections

Genotyping?

- Routine genotyping prior to receiving codeine is not being recommended for several reasons:
  - extensive metabolizers may, in some cases, convert codeine to morphine at levels similar to ultra-rapid metabolizers.
  - the positive predictive value of the test is likely low, thus the number needed to screen in order to prevent one event is very high; and
  - genotyping may be difficult to implement because preoperative lab tests are not routinely obtained before adenotonsillectomy.

Communications

- FDA Drug Safety Communication
- FDA Consumer Update
- Stakeholder outreach
- MedWatch listserv, Twitter, Facebook